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(54) Title: PREPARATION OF SUBSTITUTED OR UNSUBSTITUTED PHENYLGLYOXALS

(57) Abstract

A substituted or an unsubstituted phenylglyoxal is prepared from a corresponding substituted or unsubstituted acetophenone by oxidizing the substituted or unsubstituted acetophenone to form a corresponding substituted or unsubstituted phenylglyoxalacetal in a reactor and hydrolyzing the phenylglyoxalacetal in the same reactor to form the substituted or unsubstituted phenylglyoxal. Furthermore, the substituted phenylglyoxal is prepared from a corresponding substituted or unsubstituted acetophenone by reacting the substituted or unsubstituted acetophenone in water with a source of a nitrosonium ion in the presence of a strong acid.

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PREPARATION OF SUBSTITUTED OR UNSUBSTITUTED PHENYLGLYOXALS

RELATED APPLICATIONS

This application is related to corresponding United States Patent Application Serial No. 07/755,913 filed on September 6, 1991.

TECHNICAL FIELD OF THE INVENTION

The present invention relates to substituted and unsubstituted phenylglyoxals and, more particularly, to a method for the preparation thereof. Still more particularly, the present invention discloses methods for preparing substituted and unsubstituted phenylglyoxals from corresponding substituted and unsubstituted acetophenones.

BACKGROUND OF THE INVENTION

Substituted phenylglyoxals such as hydroxyphenylglyoxal (hereinafter referred to sometimes as "HPGO") are well known compounds that are useful in the production of intermediate products which are utilized for the preparation of pharmaceutical products. In Organic Syntheses, Coll Vol. 2, A. Blatt, ed., (1943) at p. 509, a method is disclosed for the production of unsubstituted phenylglyoxals from an acetophenone. That method uses the toxic substance selenium dioxide (SeO_2) thereby posing undesirable health hazards and disposal problems.

D. T. Manning and H. A. Stansbury, Jr., J. Am. Chem. Soc., 81, 4885-90 (1959) discloses the reaction of an unsubstituted acetophenone with nitrosyl chloride in ethanol to give a 12.4 percent yield of phenylglyoxal diethyl acetal. In addition other reaction products are generated in that reaction.

U.S. Patent No. 4,013,680 discloses a two-step method for the preparation of α-keto acids such as phenylglyoxylic acid by the oxidation of methyl ketones in aqueous solution with an inorganic nitrite salt and hydrochloric or sulfuric acid. It suggests that the reaction proceeds via the formation of a glyoxal intermediate.

U.S. Patent No. 4,272,453 discloses a method for the preparation of 1-chloro-1-ρ-methoxybenzoylformal-doxime bytheadditionofρ-methoxyacetophenone to nitrosyl chloride in carbon tetrachloride. U.S. Patent No. 3,794,620 discloses the reaction of nitrosyl chloride with aromatic acetyl derivatives. According to that patent, three moles of nitrosyl chloride are required for each acetal group.

German Patent DE 2,432,563 discloses the oxidation of substituted acetophenones using alkyl nitrites in alcohol and hydrochloric acid to prepare substituted phenylglyoxalacetals. German Patent DE 3,539,629 discloses a method of oxidizing substituted acetophenones using dinitrogen trioxide in alcohol/hydrochloric acid to prepare appropriate substituted phenylglyoxal acetals.

Copending United States patent application Serial No. 07/755,913, filed on September 6, 1991, discloses the reaction of a substituted acetophenone with a primary or a secondary alcohol in the presence of a source of a hydrogen ion (H^+) and a source of a nitrosonium ion (NO^+) to form a corresponding substituted phenylglyoxalacetal. That application, however, does not disclose the formation of the substituted phenylglyoxal.

The present invention discloses an improved method for the preparation of a substituted or an

unsubstituted phenylglyoxal from a corresponding substituted or unsubstituted acetophenone. The method involves fewer steps for the addition of reactants, avoids the use of toxic materials and complicated extraction procedures, and provides for the reaction to be carried out in one reactor.

These and other advantages and objects of the present invention will become apparent from the following description.

SUMMARY OF THE INVENTION

A substituted or an unsubstituted phenylglyoxal is prepared from a corresponding substituted or unsubstituted acetophenone, preferably, a hydroxyaromatic methyl ketone and, more preferably, 4-hydroxyacetophenone. In a first embodiment, a substituted or an unsubstituted acetophenone is reacted, in a first step, with a primary or a secondary alkyl alcohol in the presence of a source of a hydrogen ion and a source of a nitrosonium ion to form a corresponding substituted or unsubstituted phenylglyoxalacetal. The source of the hydrogen ion is a strong mineral acid such as hydrochloric acid or sulfuric acid. The source of the nitrosonium ion is an alkyl nitrite or a nitrite salt used in combination with an acid source such as sulfuric acid or hydrochloric acid or a compound NO^+X^- available from an outside source, wherein X is a halogen, a sulfite, a sulfate, phosphite or a phosphate. The substituted or unsubstituted phenylglyoxal acetal is then hydrolyzed, in a second step, in the same reactor to form the substituted or unsubstituted phenylglyoxal. Alcohol or alcohols formed during the second step are immediately removed by vaporization.

In a second embodiment, a substituted or an unsubstituted acetophenone is reacted with a source of a nitrosonium ion in water in the presence of a strong acid to form the substituted or the unsubstituted phenylglyoxal directly, in one step. The source of the nitrosonium ion is a nitrite salt which reacts with the acid to generate the nitrosonium ion in situ or a compound NO^+X^-, as defined above, which is brought in to the reactor from an external source.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, a substituted or an unsubstituted phenylglyoxal of the formula $Ar-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-R_1$ (hereinafter "Formula I") is prepared from a corresponding substituted or unsubstituted acetophenone of the formula $Ar-\overset{O}{\overset{\|}{C}}-CH_2-R_1$ (hereinafter "Formula II"). In Formulas I and II, R_1 is a straight or a branched alkyl group having 1 to 10 carbon atoms, a cycloalkyl group having 1 to 10 carbon atoms, a phenyl group, a naphthyl group, a halogen or hydrogen. Furthermore, in Formulas I and II, Ar represents an unsubstituted phenyl or naphthyl radical, a substituted phenyl radical substituted at one or more of the ortho, para, or meta positions or a substituted naphthyl radical substituted at one or more of the substitutable positions wherein the substituents to the phenyl or naphthyl radicals are independently selected from the groups of hydroxyl radicals, alkoxy radicals, acyloxy substituted radicals or unsubstituted branched or unbranched alkyl radicals R containing one to ten carbon atoms, substituted or unsubstituted phenyl radicals R_4, and substituted or unsubstituted benzyl radicals R_5. The substituted alkyl radicals R are substituted in one or more positions with radicals which are independently selected from the group of halogen, hydroxyl, sulfonic acid and sulfuric acid radicals. The substituted phenyl radicals R_4 and the substituted benzyl radicals R_5 are independently substituted in one or more positions with radicals selected independently from the group of hydroxyl radicals, sulfonic acid radicals, sulfinic acid

radicals, alkyl radicals having one to ten carbon atoms, and alkoxy radicals having one to eight carbon atoms. An example of a substituted phenylglyoxal prepared in accordance with the present invention is 4-hydroxyphenylglyoxal (hereinafter referred to as "HPGO") which is prepared from 4-hydroxy-acetophenone.

It should be noted that when R_1 is hydrogen, although the representation of the compound of Formula I is generally accepted by that formula, the more accurate structure formula thereof is the

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                O   OH
                ‖  /
formula Ar-C-CH which shows the monohydrate of the
                    \
                     OH
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substituted or unsubstituted phenylglyoxal.

In one embodiment of the invention, the substituted acetophenone is oxidized, in a first step, by reacting it with a primary or a secondary alcohol of the formula R_2-OH (hereinafter "Formula III") in the presence of a source of a hydrogen ion (H^+) and a source of nitrosonium ion (NO^+) to form a corresponding substituted phenylglyoxalacetal. The phenylglyoxalacetal is then hydrolyzed, in a second step, in the presence of an acid catalyst to form the substituted phenylglyoxal of Formula I. In another embodiment of the present invention, the substituted phenylglyoxal of Formula I is prepared in a one-step process by reacting the corresponding substituted acetophenone of Formula II with a source of a nitrosonium ion (NO^+) in an aqueous solution in the presence of a strong mineral acid.

In Formula III, R_2 is a primary or a secondary alkyl group having typically 1 to 10 carbon atoms. It should be understood that, unless stated otherwise, the

above definitions of Ar, R_1 and R_2 shall be applicable hereinafter.

The present invention is now described in more detail in the embodiments that follow.

(a) Two-Step Process for the Preparation of Substituted or Unsubstituted Phenylglyoxals

In the first embodiment, a substituted or an unsubstituted acetophenone of Formula II is converted to a substituted phenylglyoxal of Formula I in a two-step process. The two steps are carried out in sequence in the same reactor.

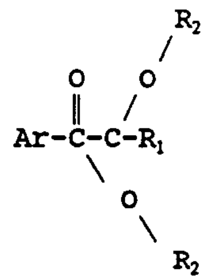
In the first step, the substituted or unsubstituted acetophenone is oxidized by reacting it with a primary or a secondary alkyl alcohol of the formula R_2-OH in the presence of a source of a hydrogen ion (H+) and a source of a nitrosonium ion (NO+) to form a corresponding substituted or unsubstituted phenylglyoxalacetal. The primary or secondary alcohol R_2-OH is typically methyl alcohol, isopropyl alcohol, sec-butyl alcohol, n-butyl alcohol or isoamyl alcohol. It is preferably present in a large excess of that amount required stoichiometrically for the reaction. In the case where the substituted acetophenone is 4-hydroxyacetophenone, the amount of alcohol R_2-OH used is from about two (2) to about ten (10) times the weight of the 4-hydroxyacetophenone or, more preferably, from about two (2) to about five (5) times the weight of the 4-hydroxyacetophenone.

The source of the hydrogen ion (H+) is a strong mineral acid, preferably hydrogen chloride or sulfuric acid. Theoretically, the acid should be present in at least a catalytic amount in the range of about 0.01 to about 0.9 moles of acid per mole of substituted or unsubstituted acetophenone; preferably, however, it

should be present in an amount of from about one (1) to about six (6) mole equivalents of the amount of the substituted or unsubstituted acetophenone such as 4-hydroxyacetophenone, more preferably, from about one (1) to about three (3) mole equivalents and, most preferably, from about one (1) to about two (2) mole equivalents.

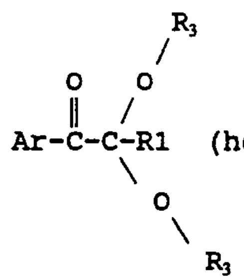
The source of the nitrosonium ion (NO+) can be alkyl nitrite of the formula R_3-O-N=O (hereinafter "Formula IV") used in combination with an acid source such as sulfuric acid, or preferably, hydrogen chloride. R_3 is an alkyl group having typically one (1) to ten (10) carbon atoms. This definition of R_3 will be applicable hereinafter, unless stated otherwise. Examples of such nitrites are methyl nitrite, ethyl nitrite or isopropyl nitrite. The alkyl nitrite R_3-O-N=O reacts with the acid to form a compound that makes the nitrosonium ion (NO+) available for the reaction and an alcohol of the formula R_3-OH (hereinafter "Formula V"). The alkyl nitrite is preferably present in an amount of from about one (1) to about five (5) mole equivalents of the amount of substituted or unsubstituted acetophenone, and, more preferably from about one (1) to about three (3) mole equivalents.

When the source of nitrosonium ion (NO+) is an alkyl nitrite of Formula IV wherein R_3 is a primary or a secondary radical, substituted or unsubstituted phenylglyoxal acetals of the formula



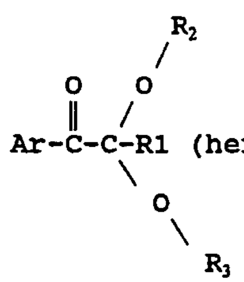
(hereinafter "Formula VI"),

the formula



(hereinafter "Formula VII"),

and



(hereinafter "Formula VIII"),

are formed. These compounds are then converted, in the second step, as described below, to the substituted phenylglyoxals of Formula I and alcohols of Formulas III and V. If R_3 is a tertiary radical group, no substituted or unsubstituted phenylglyoxal acetals of Formulas VII or VIII are formed.

The oxidation reaction is carried out in the liquid phase. It presently appears that the components of the reaction mixture used to form the substituted or unsubstituted phenylglyoxal acetals of Formulas VI, VII and VIII may be combined in any order. The reaction mixture is preferably free of water. The reaction is

exothermic and requires no heating to drive the reaction. The reaction may be cooled to a convenient working temperature. The reaction is preferably conducted at a temperature of from about -20°C to about 50°C, or more preferably from about -10°C to about 40°C or, most preferably, at about 0°C. Depending on the reaction temperature, the conversion of the substituted or unsubstituted acetophenone to the corresponding substituted or unsubstituted phenylglyoxalacetal is completed in about one (1) hour to about four (4) hours.

The source of the nitrosonium ion (NO+) can also be a nitrite salt, preferably an alkali metal nitrite salt and, more preferably, sodium nitrite. That salt in combination with the strong mineral acid, preferably hydrochloric acid or sulfuric acid, generates in situ a compound which makes the nitrosonium ion (NO+) available to the reaction. The generation of the compound NO^+X^- in situ from the nitrite salt and the acid is not preferred because it forms water in the reaction mixture.

The source of the nitrosonium ion can also be a reactant NO^+X^- which is available from a source outside of the reaction, wherein X is a halogen, an acetate, a sulfate, or a phosphate. X is preferably a halogen and, most preferably, chlorine. When the source of the nitrosonium ion is a nitrite salt or a reactant NO^+X^- which is available from an outside source, the substituted or unsubstituted phenylglyoxal acetal formed is of the Formula VI.

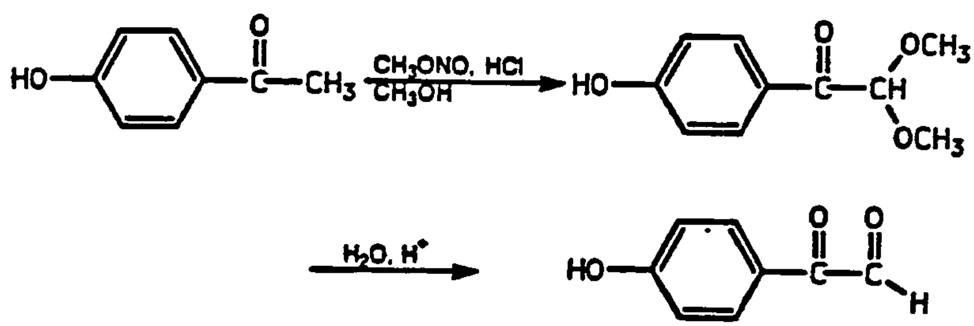
After the substituted or unsubstituted acetophenone is oxidized to form the corresponding substituted or unsubstituted phenylglyoxal acetal or acetals, as described above, the second step of the

process of the first embodiment is carried out by hydrolyzing the substituted or unsubstituted phenylglyoxal acetal or acetals so formed in the same reactor. The hydrolysis is carried out by adding water to the reaction mass. The hydrolysis step requires the presence of catalytic amounts of a strong mineral acid. In the present invention, that acid is already present in the reaction mass because it is required in the first step, i.e. the oxidation step. The products of the hydrolysis reaction are the substituted phenylglyoxals of Formula I and an alcohol or alcohols. In the case where the source of the nitrosonium ion (NO^+) is an alkyl nitrite of the Formula IV, the alcohol products are alcohols of the Formulas III and V. In the case where the source of the nitrosonium ion (NO^+) is a nitrite salt or a reactant NO^+X^- available from an outside source, the alcohol product is an alcohol of the Formula III. In order to bring the hydrolysis reaction to substantially full conversion, the alcohol product or products are being continuously removed by vaporization as they are being generated. Accordingly, the hydrolysis reaction is carried out at temperatures which are sufficiently high to vaporize the alcohol or alcohol products. Typically, the hydrolysis reaction is carried out at a temperature in the range of from about 25°C to about 100°C and, preferably, from about 50°C to about 100°C and the water is added as hot water or steam. The hydrolysis reaction is carried out for about thirty minutes to about six hours.

The substituted or unsubstituted phenylglyoxal formed falls out of the solution and can be separated therefrom by well known techniques. Furthermore, the phenylglyoxal may remain in the reaction mass and can

be used to produce further products in the same reactor.

In the case of 4-hydroxyacetophenone being converted to 4-hydroxyphenylglyoxal in the two step process where the source of the nitrosonium ion is methyl nitrite, the source of the hydrogen ion is hydrogen chloride, and the alcohol R_2-OH is methyl alcohol, the two steps of the process are represented as follows:



(b) <u>One-Step Process for The Preparation of Substituted or Unsubstituted Phenylglyoxals</u>

In the second embodiment, a substituted or an unsubstituted acetophenone of Formula II is converted to a substituted or unsubstituted phenylglyoxal of Formula I in a one-step process. The substituted acetophenone, such as 4-hydroxyacetophenone, is reacted with a source of nitrosonium ion in water in the presence of a strong mineral acid. It should be understood that, in this embodiment, Ar, which was previously defined, should be such that the compound of Formula II is sufficiently soluble in water to provide

sufficient contact between the reactants for the reaction therebetween to proceed.

The source of a nitrosonium ion is a compound NO+X- wherein X is a halogen, a sulfite, a sulfate, a phosphite or a phosphate. X is preferably a halogen and, most preferably, chlorine. The reactant NO+X- can be available from an outside source or, preferably, can be generated in situ by reacting a nitrite salt, preferably an alkali metal nitrite salt and, more preferably, sodium nitrite, with a strong acid such as hydrochloric acid or sulfuric acid.

In the case in which sodium nitrite is reacted with hydrochloric acid to generate a source of nitrosonium ion (NO^+) in situ and the source of nitrosonium ion is reacted with a substituted or an unsubstituted acetophenone of Formula II such as 4-hydroxyacetophenone, the primary reactions are as follows:

$$NaNO_2 + HCl \longrightarrow HONO + NaCl \qquad \text{(Reaction 1)}$$

$$HONO + HCl \longrightarrow NOCl + H_2O \qquad \text{(Reaction 2)}$$

$$Ar\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}CH_3 + 2NOCl \longrightarrow Ar\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}H + N_2O + 2HCl \qquad \text{(Reaction 3)}$$

Reaction 3 shows that two (2) mole equivalents of a nitrosonium ion (NO+) are required stoichiometrically to convert one (1) mole equivalent of substituted or unsubstituted acetophenone. Therefore, at least two moles of sodium nitrite are required to generate the stoichiometric requirements of nitrosonium one (NO+) to effect maximum conversion of the substituted or unsubstituted acetophenone. Satisfactory conversions, however, are obtained with lower amounts of nitrite salt. Accordingly, the reaction is carried out by using from about one (1) to about three (3) and

preferably, about 2.2 moles of sodium nitrite per mole of substituted or unsubstituted acetophenone and from about one (1) to about ten (10) and, preferably, about six (6) moles of hydrochloric acid per mole of substituted or unsubstituted acetophenone. The reaction is carried out at a temperature in the range of about 30°C to about 90°C and, preferably, in the range of about 40°C to about 65°C.

In the conversion of the substituted or unsubstituted acetophenone, certain side reactions compete with Reaction 3. For example, in the case wherein 4-hydroxyacetophenone is converted, side reactions form 4-hydroxybenzoyl formic acid and 4-hydroxybenzoic acid. In order to minimize the side reactions and the loss of NOCl, it is preferred that the sodium nitrite in an aqueous solution be added gradually to an aqueous solution of substituted or unsubstituted acetophenone and hydrochloric acid over a period of about 0.5 to about ten (10) hours and, more preferably, over a period of about one (1) to four (4) hours.

Without limiting the scope of the invention, it is hypothesized that the Reaction 3 is carried out by going through several intermediates to eventually form the substituted or unsubstituted phenylglyoxal. In the case, for example, of the conversion of 4-hydroxyacetophenone, the first equivalent of NOCl which is generated by the reaction of sodium nitrite with hydrochloric acid reacts with the enol form of 4-hydroxyacetophenone to produce a nitroso compound which then tautomerizes to 4-hydroxy-α-isonitroso-acetophenone (hereinafter "HINAP"). The HINAP then reacts with the second molecule of NOCl to form an intermediate which is attacked by a molecule of water

and which by proton transfer forms another intermediate. The latter loses N_2O and H_2O to form hydroxyphenylglyoxal.

The following examples further illustrate the invention but are not to be construed as limitation on the scope of the invention contemplated herein.

EXAMPLE 1

Preparation of 4-Hydroxyphenylglyoxal in an Alcohol Solution (Two-Step Process)

Approximately 0.808 moles of methylnitrite were added to a solution containing 50 grams (0.3672 moles) of 4-hydroxyacetophenone in 200 milliliters of methanol and 8 grams of hydrocholoric acid (HCL). The reactor was stirred during the reaction and for a short time following addition of the methylnitrite. Following completion of the oxidation, the reactor was allowed to cool to about 30 °C. 400 milliliters of distilled water were added to the flask and distilled into a Dean-Stark trap.

After removal of 400 milliliters by distillation, another 400 milliliters of water were added to the reactor. The solution was heated to 60° and 48.03 grams of concentrated HCl were added. After about sixty (60) minutes, the reactor was cooled, yielding a 65 percent yield of 4-hydroxyphenylglyoxal in an aqueous solution.

EXAMPLE 2

Preparation of 4-Hydroxyphenylglyoxal in Aqueous Solution (One-Step Process)

A solution of 45.5 grams (0.66 moles) of $NaNO_2$ in 130 milliliters of water was added over a period of four (4) hours to a warm (60°C) solution comprising 40.8 grams (0.3 moles) of 4-hydroxyacetophenone in 200 milliliters of 6N aqueous HCl. The solution was maintained at 60°C

throughout the addition. The rate of addition of the $NaNO_2$ solution is shown in the table below:

Time (min) (milliliters)	Volume of $NaNO_2/H_2O$
0	0
30	40
75	60
120	100
240	150

After completion of the addition the reaction mixture was cooled to 10°C, whereupon the HPGO precipitated out of solution. The solid was filtered and dried to give fifty percent yield of HPGO.

While the invention is described with respect to specific embodiments, modification thereof can be made by one skilled in the art without departing from the spirit of the invention. The details of said embodiments are not to be construed as a limitation except to the extent indicated in the following claims.

What is claimed is:

1. A method of preparing a substituted or unsubstituted phenylglyoxal from a corresponding substituted or unsubstituted acetophenone, comprising the steps of:

oxidizing the substituted acetophenone to form a corresponding substituted or unsubstituted phenylglyoxalacetal in a reactor; and

hydrolyzing the phenylglyoxalacetal in the reactor to form the substituted or unsubstituted phenylglyoxal.

2. The method according to claim 1 wherein the oxidizing step includes the step of reacting the substituted or unsubstituted acetophenone with a primary or a secondary alcohol in the presence of a source of nitrosonium ion and a source of hydrogen ion.

3. The method according to claim 1 wherein the oxidizing step is carried out at the temperature of a range of about -20°C to about 50°C.

4. The method according to claim 1 wherein the hydrolyzing step is carried out at a temperature in the range from about 60°C to about 100°C.

5. The method according to claim 1 further including the steps of forming an alcohol in the hydrolyzing step and vaporizing the alcohol to remove the alcohol from the reactor.

6. The method according to claim 1 further including the step of adding an alkyl nitrite to the reactor prior to the oxidizing step.

7. The method according to claim 2, wherein the source of nitrosonium ion is a compound of the formula NO+X- wherein X is a halogen, an acetate, a sulfate, or a phosphate.

8. The method according to claim 1 wherein the substituted phenylglyoxal is a compound of the

formula $\mathrm{Ar}-\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}-R_1$ and is prepared from a corresponding substituted acetophenone of the formula $\mathrm{Ar}-\overset{\overset{O}{\|}}{C}-CH_2-R_1$ wherein R1 is an alkyl group having 1 to 10 carbon atoms, a cycloalkyl group having 1 to 10 carbon atoms, a phenyl group, a naphthyl group, a halogen or hydrogen, and wherein Ar is an unsubstituted phenyl or naphthyl radical, a substituted phenyl radical substituted independently at one or more of the ortho, para, or meta positions or a substituted naphthyl radical substituted independently at one or more of the substitutable positions.

9. The method according to claim 8 wherein the substituted phenyl radicals or the substituted naphthyl radicals are substituted with substituents which are independently a hydroxyl radical, an alkoxy radical, an acyloxy radical, a substituted or unsubstituted branched or unbranched alkyl radical R containing one to ten carbon atoms, a substituted or an unsubstituted phenyl radical R_4 or a substituted or unsubstituted benzyl radical R_5.

10. The method according to claim 9 wherein the substituted alkyl radical R is independently substituted in one or more positions with a halogen, a hydroxyl radical, a sulfonic acid radical, or a sulfuric acid radical and the substituted phenyl radical R_4 and the substituted benzyl radical R_5 are independently substituted in one or more positions with a hydroxyl radical, a sulfonic acid radical, a sulfinic acid radical, an alkyl radical R_6 having one to ten carbon atoms or an alkoxy radical having one to eight carbon atoms.

11. A method of preparing a substituted or an unsubstituted phenylglyoxal from a corresponding substituted or unsubstituted acetophenone, comprising the

step of reacting the substituted acetophenone in water with a source of a nitrosonium ion in the presence of a strong acid.

12. The method according to claim 11 wherein the source of nitrosonium ion is a compound of the formula NO+X- wherein X is a halogen, a sulfate, or a phosphate.

13. The method according to claim 11 wherein the source of the nitrosonium ion is a nitrite salt.

14. The method according to claim 11 wherein the substituted or unsubstituted phenylglyoxal is a compound of the formula $Ar-\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}-R1$ and the substituted or unsubstituted acetophenone is of the formula $Ar-\overset{\overset{O}{\|}}{C}-CH_2-R_1$ wherein R_1 is an alkyl group having 1 to 10 carbon atoms, a cycloalkyl group having 1 to 10 carbon atoms, a phenyl group, a naphthyl group, a halogen or hydrogen, and wherein Ar is a an unsubstituted phenyl or naphthyl radical substituted phenyl radical substituted independently at one or more of the ortho, para, or meta positions or a substituted naphthyl radical substituted independently at one or more of the substituted positions.

15. The method according to claim 14 wherein the substituted phenyl radicals or the substituted naphthyl radicals are substituted with substituents which are independently a hydroxyl radical, or a alkoxy radical, an acyloxy radical, a substituted or unsubstituted branched or unbranched alkyl radical R containing one to ten carbon atoms, a substituted or unsubstituted phenyl radical R_4 or a substituted or unsubstituted benzyl radical R_5.

16. The method according to claim 15 wherein the substituted alkyl radical R is independently substituted in one or more positions with a halogen, a hydroxyl radical, a sulfuric acid radical or a sulfuric acid

radical and the substituted phenyl radical R_4 and the substituted benzyl radical R_5 are independently substituted in one or more positions with a hydroxyl radical, a sulfonic acid radical, a sulfinic acid radical, an alkyl radical R_6 having one to ten carbon atoms or an alkoxy radical having one to eight carbon atoms.

17. The method according to claim 14 wherein R_1 is hydrogen.

INTERNATIONAL SEARCH REPORT

PCT/US93/01348

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07C 45/28
US CL :568/315

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 568/315

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE,A, 2,432,563 (Wirth et al.) 27 February 1975 See entire document.	1-17
A	US,A, 3,794,620 (Bateman) 26 February 1974 See entire document.	1-17
A	US,A, 4,013,680 (Godfrey et al.) 22 March 1977 See entire document.	1-17
A	US,A, 4,272,453 (Booth et al.) 09 June 1981 See entire document.	1-17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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Date of the actual completion of the international search	Date of mailing of the international search report
08 APRIL 1993	10 MAY 1993
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